Remarks

Claims 1, 2, 6-16, 18 and 20-29 are pending. Claims 2 and 16 have been canceled. Claims 1, 14, 15, and 28 have been amended. Claims 1 and 15 have been amended to specify that the DNA construct contains a 3' termination sequence comprising a polyadenylation signal following the last coding sequence. Support for this amendment can be found on page 2, line 30 to page 3, line 2 of the specification. Claim 28 has been amended for claim language. Claims 14 and 28 have been amended to recite "marker proteins". Support for this amendment can be found on page 12, lines 13-28. The specification has been amended to correct a typographical error.

Rejection Under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-2, 6-16, 18, and 20-29 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003; *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993);

See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for examples.

Claims 1, 6-15, 18 and 20-29 satisfy the enablement requirement

Claim 1 is directed to a DNA construct for expressing multiple gene products that includes a promoter, multiple genes to be expressed (exteins), intein sequences to catalyze excision of the exteins and a 3' termination sequence following the last coding sequence comprising a polyadenylation signal. The specification teaches how to make this DNA construct on pages 18 and 19. The specification also teaches intein sequences that prevent ligation of the cleaved exteins (page 7, line 29 to page 8, line 19) as well as the reasons for modifying the intein sequences.

A proper analysis of the factors described in *In re Wands* shows that these claims satisfy the enablement requirement. The quantity of experimentation necessary to make and use the claimed DNA construct is **not undue**. All of the methods described are well known and routine to one of ordinary skill in genetic engineering. Experimentation is clearly necessary in the field of genetic engineering but it is critical to note that one of ordinary skill in this field is able to undertake a task such as modifiying sequences, ligating sequences in a DNA construct and expressing the construct in a host cell without *undue* experimentation. There is sufficient direction and guidance given by the specification to make and express the claimed DNA construct. The process of making the DNA construct and which sequences to use is described on pages 4-12 of the specification and in Example 1. The experimental protocols are routine in the art and expression vectors, restriction enzymes and ligation enzymes are commerically available.

On page 7, lines 11-28, the specification discloses that the mechanism of the protein splicing process has been studied in great detail and **conserved** amino acids have been found at the intein and extein splicing points. In addition, the specification states that intein sequences are well known and cataloged on the web. The disclosure also teaches on page 9, lines 6-23 that mutagenesis of the C-terminal extein junctions in the *Pyroccoccus* species GB-DNA polymerase intein and in the *Mycobacterium xenopi* Gyra intein produces altered splicing elements that induce cleavage of the polyproteins but prevent subsequent ligation of the exteins. Accordingly, one of ordinary skill in the art would be able to modify equivalent residues of other intein splicing units to prevent extein ligation due to the **conservation** of amino acids at the C-terminal extein junction. Methods to modify nucleotide sequences are established and the sequences themselves are well-known. The courts have indicated that some experimentation is permitted as long as such experimentation is not undue. As stated in *MIT v. A.B. Fortia*, "The fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation".

Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-2, 6-16, 18, and 20-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed". *Wertheim*, 541 F.2d at 262, 191 USPQ at 96 (CCPA 1976). The written description requirement for a claimed genus may be satisfied through a sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or a disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be a situation where one species adequately supports a genus. See, e.g., *Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326-27.

The Federal Circuit has **overturned** the application of the written description requirement set out in *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir.1997). In the patent context, not all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if, in the knowledge of the art, the disclosed function is

sufficiently correlated to a particular, known structure. (*Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 Fed.Cir. 2003). In addition, in a separate case, the Federal Circuit held that "reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of (35 U.S.C.) § 112, 1." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002) ("*Enzo I*") *rev'd on rehearing*, 323 F3d 956 (2002) ("*Enzo II*").

Claims 1, 6-15, 18 and 20-28 satisfy the written description requirement

The claims are directed to using "modified intein sequences". The specification clearly describes on page 7-9 how to use available inteins (see page 8) for use in the claimed method. The method for making and using the claimed DNA construct is explicitly described in Example 1 on page 18 of the specification. The genus of inteins is sufficiently described by the specification. The database of known inteins and their sequences, which is highly accessible to the public and may be considered a public depository, is described on page 7, lines 18-21. Inteins that prevent ligation of cleaved exteins are also described. For example, the intein from *Mycobacterium xenopi* GyrA and inteins modified by mutating serine 538 to alanine or glycine are described on page 8, lines 1-9. It has been stated in *Rasmussen* and recently affirmed in *Amgen* that it is not necessary to disclose the sequences of all claimed inteins in a genus.

The mechanisms of intein-mediated cleavage and the sequences responsible for cleavage are also known in the art. Due to the ample description of the inteins and the reference to the

intein database, one of skill in the art would read the specification and clearly determine that the Applicants were in possession of the claimed methods and DNA constructs at the time of filing.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 14 and 28 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Rejection Under 35 U.S.C. § 102

Claims 1, 6, 8, 10-11, 15, 20, 22, and 24-25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Xu et al. The EMBO Journal 15(19): 5146-5153 (1996) ("Xu 1996") in view of Xu et al. Cell 75: 1371-1377 (1993) ("Xu 1993"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

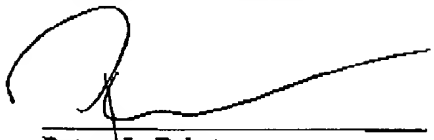
The claims have been amended to specify that the DNA constructs contain a 3' termination sequence following the last coding sequence comprising a polyadenylation signal. There is no teaching or suggestion of a polyadenylation signal in either of the Xu references.

Claim Objections

Claims 2 and 16 were objected to for spelling and grammar errors. Applicants respectfully traverse this objection to the extent that it is applied to the claims as amended.

Allowance of claims 1, 6-15, 18 and 20-29 is respectfully solicited.

Respectfully submitted,



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U.S.S.N. 09/779,957
Filed: February 9, 2001
AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, **June 9, 2004**, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

~~Hershey Miller~~
Brian Adams

Date: **June 9, 2004**